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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/937,840	SOON-SHIONG ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-129* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-129* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 75-129 ARE PRESENTED FOR EXAMINATION

Applicants' amendment and Information Disclosure Statement filed 9/4/2007 have been received and entered into the application. Accordingly, claims 15-17, 20-25, and 48-74 have been cancelled and claims 75-129 have been added. Also, as reflected by the attached, completed copy of USPTO Form 1449 the cited references have been considered.

Applicants' arguments, filed 9/4/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The prosecution history of the present application is complicated due in part to the case being transferred to a different Examiner and also due to the present Examiner indicating some subject matter as allowable in the Office Action mailed 4/4/2007. Claims 1-17, drawn to methods and compositions comprising sub-therapeutic dose levels of active agents were originally presented for prosecution (see claim set submitted 1/28/2002). The original Examiner required election of a single specie of active agent in the Requirement for Election mailed 12/22/2003. In response, Applicants elected "chemotherapeutic drugs" as the active agent and intravenous as the route of administration (see Response filed 1/22/2004). Applicants also submitted new claims 18-21 in said response. In the Non-Final rejection mailed 5/26/2004, the Examiner withdrew the requirement to elect a specific mode of administration and maintained the requirement to elect a genus of therapeutic agent. Claims 1-21 were rejected under 35 U.S.C.

§ 112, 1st Paragraph (Scope of Enablement) as being enabled for sub-therapeutic administration of paclitaxel in the treatment of paclitaxel-responsive cancer, but not enabled for the treatment of all types of cancer using any chemotherapeutic agent. This rejection was withdrawn in the Final Rejection mailed 11/17/2004. In subsequent prosecution, including the filing of an RCE (3/16/2005) and a Non-Final rejection (6/9/2005), various art rejections were made and additional claims submitted for examination.

When the present Examiner took over prosecution, claims 1-5, 7-14, 18-19, and 26-47 (methods) and claims 15-17 and 20-25 (compositions) were under examination (see claim set submitted 12/8/2005). In the Non-Final rejection mailed 8/23/2006, the Examiner rejected method claims 1-5, 7-14, 18-19, and 26-47 as lacking enablement under 35 U.S.C. § 112, 1st Paragraph and indicated the unit dosage form of claims 15-17 and 20-25 as allowable. In an effort to advance prosecution, Applicants cancelled method claims 1-5, 7-14, 18-19, and 26-47 in the response filed 12/21/2006. Upon further consideration of the pending composition claims (claims 15-17, 20-25, and 48-74), the Examiner mailed a Non-Final rejection on 4/4/2007.

Newly submitted claims 75-129 are drawn to methods of administering paclitaxel to a subject. Because both method claims and composition claims were examined in previous prosecution, the response is deemed responsive to the Non-Final rejection mailed 4/4/2007. However, as indicated to Jian Xiao in a telephone call, the rejections set forth in the present Office Action are made final because they are necessitated by Applicants' amendments.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 9/4/2007. The Examiner has considered the references cited therein to the extent that each is a proper citation. Reference 64 (Rote Liste 1999) was not considered because it is not in English and no translation has been provided. Please see the attached USPTO Form 1449.

Claim Interpretation

Claim 90 recites administration of an amount of paclitaxel "*about* 1% to *about* 20% of the conventional dose of paclitaxel over the same period". Dependent claim 93 recites an amount of paclitaxel "*about* 1% to *about* 10% of the conventional dose of paclitaxel". Dependent claim 94 recites an amount of paclitaxel "*about* 1% to *about* 5% of the conventional dose of paclitaxel". Independent claim 111 and dependent claim 113 recite similar limitations with respect to the claimed doses of paclitaxel. While the limitation "about" as recited in the instant claims has been held by the courts to comply with the provisions of 35 U.S.C. § 112, 2nd paragraph, the instant specification does not define to what extent the recited "about" modifies the claimed ranges. As such, the claims reasonably encompass administration of paclitaxel in any dose. Support for this interpretation is found in the specification at pages 8-9 wherein Applicants teach that acceptable values for the claimed sub-therapeutic doses are in the range of "from about 1% to less than about 98% of the amount of pharmacologically active agent conventionally administered" and that the corresponding upper end point of the sub-therapeutic dose amount range is generally "less than or equal to about 99% of the amount of pharmacologically active agent conventionally administered".

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 75-89 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility. To satisfy 35 U.S.C. § 101, an invention must be "useful." Courts have recognized that the term "useful" used with reference to the utility requirement can be a difficult term to define; however, Courts have used the labels "practical utility," "substantial utility," or "specific utility" to refer to this aspect of the "useful invention" requirement of 35 U.S.C. § 101. A "specific utility" is specific to the subject matter claimed and can "provide a well-defined and particular benefit to the public." *In re Fisher*, 421 F.3d 1365, 1371, 76 USPQ2d 1225, 1230 (Fed. Cir. 2005). As the claims point out, the application relates to methods of administering paclitaxel "to a subject". According to Applicants' specification, the administration methods of the invention are useful for the treatment of cancer in a subject (see pages 2-4 of specification). Applicants predicate patentability of their claimed methods partially on the advantage "sub-therapeutic" dose levels of paclitaxel have in reducing toxicity while maintaining clinical efficacy. In this regard, the specification states, *inter alia*:

> Thus, there is a need for methods of administration of pharmacologically active agents (especially chemotherapeutic drugs) which can achieve therapeutic levels of the pharmacologically active agent over more than a few days (i.e., more than 2-4 days).
>
> In addition, there is a need for methods of administration of pharmacologically active agents (e.g., chemotherapeutic drugs) which do not cause unnecessary toxicity reactions and adverse events in a subject being treated due to the presence of substantially higher than therapeutic levels (e.g., levels that are cytotoxic to tumor cells in the subject being treated for a cancer) of the pharmacologically active agent
>
> Invention methods comprise administering to the subject sub-therapeutic dose levels (i.e., very low levels, such as levels below the conventionally accepted therapeutic dose) of a

> pharmacologically active agent effective against the infirmity. Surprisingly, it has been found that continuously administering pharmacologically active agents (especially chemotherapeutic agents) effective against infirmities at sub-therapeutic dose levels over long or extended periods is efficacious in the treatment of these infirmities.
>
> In accordance with the present invention, there are provided methods for the treatment of a subject having an infirmity. Invention methods comprise administering to the subject sub-therapeutic dose levels of a pharmacologically active agent effective against the infirmity.
>
> Sub-therapeutic dose levels contemplated for use in the practice of the present invention include actual levels of pharmacologically active agent (e.g., plasma levels for systemic administration, and infirm tissue levels for localized administration) that are lower than conventionally accepted plasma levels considered essential for successful treatment of the infirmity when the pharmacologically active agent is administered by conventional means (e.g., by continuous IV infusion or bolus injection).

Thus, the claimed administration methods are set forth as therapeutics that will be administered to patients so as to affect some biological response (*e.g.*, the treatment of cancer). However, while Applicants have set forth the utility of the claimed compositions with reasonable specificity (*i.e.*, for the treatment of cancer and for reducing toxicity), they have not set forth a *substantial* utility. In this regard, a substantial utility is one in which the claimed method will reasonably achieve the intended result – in this case, the treatment of cancer. At the present time however, there is no evidence of record that would indicate that administration of a "sub-therapeutic dose" over a long period of time would have the utility set forth in the specification. For example, at page 2 of the specification, it is indicated that plasma levels of 0.5-1.0 μg/mL paclitaxel are required for a cytotoxic effect and that *in vitro* studies indicate that paclitaxel is active in the 0.5 μg/mL range. However, claims 75-89 recite administration of paclitaxel wherein the plasma level of paclitaxel in a subject is maintained at 0.01-0.05 μg/mL over a period of 7 days or more. It is not seen how doses that are 10-50x lower than therapeutic levels can have any beneficial anticancer effect, even if administered for an indefinite time period. A

sub-therapeutic level is just that: below a therapeutic level. Meaning, the amount being administered is, by definition, not therapeutically effective. "[A]n application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the 'substantial' utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public." *Fisher*, 421 F.3d at 1371, 76 USPQ2d at 1230. In the instant case, the methods of administering sub-therapeutic doses of paclitaxel fail to provide an immediate benefit to the public because it is not apparent that the claimed administration methods will have the biological affects alleged in the specification. As such, the instant invention appears to be, at this time, a mere scientific curiosity. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Accordingly, the Examiner cannot accept the alleged utility of the claimed methods absent clear and convincing proof thereof.

The presently claimed methods of administering paclitaxel have been alleged to be useful for the treatment of any and all cancers. However, nowhere in the specification have Applicants demonstrated the alleged biological activity of the claimed administration of sub-therapeutic dose levels (*i.e.*, 0.01-0.05 μg/mL) of paclitaxel. Thus, it is not seen what benefit the claimed methods would have in the treatment of a human patient if the skilled artisan would have to carry out all of the experimentation necessary to determine whether long-term administration of sub-therapeutic dose levels of paclitaxel has any benefit in the treatment of cancer.

Thus, in the absence of clear and convincing proof that the claimed methods have therapeutic use in treating human patients, it is the Examiner's position that the instantly claimed

invention lacks a substantial utility. It is simply not reasonable to accept Applicants' assertion that long-term administration of paclitaxel that results in plasma levels 10-50x lower than the plasma levels that are required for clinical efficacy will have any beneficial utility in treating cancer in a human patient.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-89 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement rejection.

Because the claims lack a substantial utility as set forth above, they also lack enablement *a priori*.

Claims 90-129 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for administering paclitaxel at or near "conventional doses" over 7 days or more, does not reasonably provide enablement for administering paclitaxel at dose levels 1-20% or 1-10% of the conventional dose of paclitaxel (*i.e.*, at dose levels that would likely result in sub-therapeutic plasma levels of paclitaxel). The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

The nature of the invention: The invention relates to methods that reasonably encompass administration of "sub-therapeutic levels" of paclitaxel. Such methods comprise administering dose levels of paclitaxel that are 1% to 20% or 1% to 10% of the "conventional dose" to a subject (*i.e.*, "sub-therapeutic" doses). The specification and claims indicate that administration of paclitaxel in sub-therapeutic doses over 7 days or more can be used to treat cancer.

Relative skill of those in the art: The relative skill of those in the art is high, generally that of an M.D. or Ph.D.

State and predictability of the art: The art of treating cancer and determining appropriate administration regimens and dose levels is prima facie unpredictable.

> The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention.

> If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. See M.P.E.P. 2164.03

As illustrative of the state of the art, the examiner cites Herben *et al.* (J. Clin. Oncol., 1999, vol. 17, pages 1897-1905) (previously cited). This article plainly demonstrates that the art of low-dose, continuous chemotherapy is very unpredictable. As discussed in Herben *et al.*, patients with solid tumors received continuous infusions of irinotecan for 14, 17 and 21 consecutive days (Abstract). The starting dose was 175 mg/m^2 (*i.e.* 12.5 mg/m^2/day). This dose represented 50% of the recommended dose with a schedule of once every 3 weeks (page 1898). As shown in Table 3 (page 1900), gastrointestinal toxicity varied greatly with the different dose levels. Further, the pharmacokinetic parameters of irinotecan also varied with different dose levels and were also very different than the pharmacokinetics of irinotecan when administered "conventionally" (Table 4, page 1901). Because of toxicity, an actual dose-intensity of 125.7 mg/m^2/3 weeks was achieved which is 40% of the dose-intensity obtained with short infusion schedules of irinotecan (page 1903). The authors conclude, "The optimal administration schedule of irinotecan in the clinic is still uncertain" (page 1904).

The unpredictability of the present invention is further compounded by the fact that Applicants contemplate treating cancer with a sub-therapeutic dose of paclitaxel. By definition, a sub-therapeutic dose will not be clinically effective. If a particular dose is effective in treating cancer then it is, by definition, a therapeutic dose. Munoz *et al.* (The Breast, 2005, vol. 14, pages

466-479) (previously cited), cited for evidentiary purposes only, further highlight this fact. The authors state that a "major handicap" of "metronomic chemotherapy" is the determination of an optimal biologic "low" dose for any given chemotherapy regimen (page 475). Because many new drugs do not have dose-limiting toxicities or express optimal therapeutic activity below a MTD, this "greatly increases the empiricism associated with using these drugs in clinical trials, and hence the probability of obtaining negative results" (page 475).

Yet another example of the unpredictability of low-dose continuous chemotherapy is found in Blumenreich *et al.* (Am. J. Clin. Oncol., 1994, vol. 17, pages 163-165) (previously cited). This reference discloses that etoposide is more active in small cell lung cancer when given over 5 days than as a single injection. The authors wished to examine this concept further by administering a dose of 50 mg by mouth daily. The median duration of therapy was 63 days. Out of 19 patients, 13 patients had progression of disease. No complete or partial responses were observed. The authors conclude, "low-dose continuous oral etoposide is a well-tolerated but ineffective regimen in non-small cell lung cancer" (Abstract).

Long-term continuous infusions of chemotherapeutic agents are well known in the art. For example, Sorensen *et al.* (Acta Oncologica, 1999, vol. 38, pages 1043-1045) (previously cited) describe the long-term continuous infusion of 5-fluorouracil (5-FU) in patients with head and neck cancer (Abstract). The dose administered was 300 mg/m^2/day for a maximum of 16 weeks. Even at this dose, there was only an objective response rate of 15% in 41 patients. The authors conclude, "[L]ong-term continuous infusion of 5-FU had only modest activity in terms of response rate" (page 1044). Given that a therapeutic dose (in this case, 300 mg/m^2/day), continuously administered over 16 weeks, demonstrated only "modest activity" (15% response),

it is not at all predictable (and highly unlikely) that administration of a sub-therapeutic dose over an extended period of time will effectively treat cancer.

Clearly then, the treatment of cancer with therapeutic doses and "low-doses", let alone sub-therapeutic doses of an active agent, particularly in humans, is extremely unpredictable.

The breadth of the claims: The claims are broad, insofar as they recite administration of paclitaxel in doses ranging from "about 1% to about 20%" and "about 1% to about 10%" of the conventional dose of paclitaxel over a period of more than 7 days. Thus, only very general, broad guidance with respect to the administration of sub-therapeutic doses of paclitaxel is provided by the specification.

The amount of direction or guidance provided and the presence or absence of working examples:

> The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The specification provides only very general direction and guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat all cancers, particularly in humans, and more particularly using "sub-therapeutic" doses of active agents. No "working examples" are presented in the specification. However, pages 18-19 of the disclosure describe the administration of paclitaxel in the treatment of "cancers responsive

to paclitaxel". Even here, only a broad dose (50-150 mg/m^2) is described and this example is prophetic in nature (*i.e.* the efficacy of this administration regimen has not been demonstrated for any cancer). No reasonably specific guidance is provided concerning useful therapeutic protocols for treating cancer.

The quantity of experimentation necessary: Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed methods could be predictably used as treatments for cancer as contemplated by the specification. Further, the skilled artisan would not, *a priori*, have a reasonable expectation that administering a "sub-therapeutic" dose, no matter how long the administration, would be effective in treating cancer. A sub-therapeutic dose is just that, below the therapeutic level. Examiner respectively submits that, by definition, a sub-therapeutic dose cannot treat cancer. If any particular dose does treat cancer, it is a therapeutic dose. While claims 90-129 recite that a "therapeutically effective plasma level of paclitaxel in the subject is maintained throughout the 7 days or more", there is no evidence of record that therapeutically effective plasma levels of paclitaxel can be achieved *via* administration of 1% to 20% or 1% to 10% of the "conventional dose" of paclitaxel over the same period of time.

It is the examiner's position that the skilled artisan, presented with the instant disclosure, would have to engage in undue experimentation to practice the claimed invention. It is not routine experimentation to treat cancer with sub-therapeutic doses of active agents. The art of treating cancer with therapeutic doses of chemotherapeutic agents is itself generally

unpredictable. Even in the case of an agent known to treat a particular cancer, the therapeutic dose and administration schedule of that particular agent cannot be readily predicted from *in vitro* or *in vivo* efficacy data.

In the instant case, to treat cancer with sub-therapeutic doses of active agents is even more unpredictable than treating cancer with doses of an agent known to be effective in the treatment of a particular cancer. For example, the pharmacokinetics of a chemotherapeutic agent will vary greatly with different administration schedules. The skilled artisan is faced with the task of determining an administration schedule and dose that effectively treats cancer (*i.e.* is therapeutic) but does not exhibit unwanted and/or intolerable toxicity.

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff 'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

In the instant case, the art does not *routinely* administer chemotherapeutic drugs in sub-therapeutic doses.

Given the above *Wands* factors analysis, although the specification discloses broad doses (about 1 to about 20% of "conventionally administered" doses) and administration schedules ("from about 7 days to about 1 year"), the instant specification does not provide the skilled artisan with sufficient guidance with respect to treating cancer with doses of paclitaxel that would likely result in sub-therapeutic plasma levels of the drug. With respect to oral administration as recited in claims 96 and 115, WO 98/53811 (previously cited by Examiner) teaches that paclitaxel is poorly absorbed when administered orally (less than 1%) and

researchers have shown that paclitaxel has a bioavailability of 0% upon oral administration. Further, oral dosing with paclitaxel does not seem possible "since no evidence of antitumor activity was found on oral administration up to 160 mg/kg/day (page 3, lines 8-18). Thus, it is clear that oral administration of paclitaxel is not enabled by the instant disclosure. With respect to the claimed "microspheres" as recited in claims 102 and 121, WO 99/00113 (Reference 47 on IDS filed 9/4/2007) teaches that known procedures for preparing microspheres are not capable of entrapping water-insoluble drugs such as paclitaxel. The limitations are inherent in the technique of preparation (page 7, lines 14-25). Applicants have not provided any novel methods of preparing paclitaxel-containing microspheres that may overcome the limitations of the prior art methods.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). In this case, Applicants have provided no evidence that administering paclitaxel in the claimed dose ranges, which are below those that are known in the art to be clinically effective, have any clinical efficacy in the treatment of cancer. Nor have Applicants provided the skilled artisan with any reasonably specific guidance with respect to the particular doses and length of administration of paclitaxel.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 90-91, 93-95, 97-98, 100, 103, 105-114, 116-117, 119, 122, and 124-129 are rejected under 35 U.S.C. § 102(b) as being anticipated by Chang *et al.* (Reference 55 on IDS filed 9/7/2007).

The instant claims recite methods of administering paclitaxel comprising administering paclitaxel over a period of "7 days or more", wherein the amount of paclitaxel is "*about* 1% to *about* 20% of the conventional dose" of paclitaxel (claim 90) or "*about* 1% to *about* 10% of the conventional dose" of paclitaxel (claim 111).

Chang *et al.* teach a dose escalation study of paclitaxel wherein patients were treated with a one-hour infusion of paclitaxel weekly for 3 weeks. An infusion meets the limitation "systemically" and "intravenously" as recited in claims 95, 97, 114, and 116. A "one-hour infusion" meets the limitation "continuously" as recited in claims 106 and 125. The administration of paclitaxel weekly for 3 weeks meets the limitations of claims 107-109 and 126-128, which recite administration over periods of less than one year, less than 3 months, and less than one month. With respect to dose, Chang *et al.* administered paclitaxel at a dose of 50 mg/m^2/week, increasing 10 mg/m^2/week every five patients. These doses meet the limitation of claims 105 and 124, which recite a conventional dose of paclitaxel of 135-175 mg/m^2 over a period of three weeks.

As discussed *supra*, the claims reasonably encompass administering a dose that is "*about* 99%" of the conventionally administered dose. Accordingly, the claims are deemed properly rejected as being anticipated by Chang *et al.*

Claims 90-95, 97-98, 100, 103, 105-108, 110-114, 116-117, 119, 122, 124-127, and 129 are rejected under 35 U.S.C. § 102(b) as being anticipated by Klaassen *et al.* (Reference A28 on IDS filed 5/12/2003).

The instant claims recite methods of administering paclitaxel comprising administering paclitaxel over a period of "7 days or more", wherein the amount of paclitaxel is "about 1% to about 20% of the conventional dose" of paclitaxel (claim 90) or "about 1% to about 10% of the conventional dose" of paclitaxel (claim 111).

Klaassen *et al.* teach administration of paclitaxel via a 1-hour infusion on days 1, 8, 15, 22, 29, and 36 (every 50 days) at dose levels of 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, and 100 mg/m^2, thus meeting the limitations of claims 90-95, 97, 105-108, 110-114, 116, 124-127, and 129.

Claims 90-95, 97-98, 100, 103, 105-108, 110-114, 116-117, 119, 122, 124-127, and 129 are rejected under 35 U.S.C. § 102(b) as being anticipated by Fennelly *et al.* (Reference A16 on IDS filed 5/12/2003).

The instant claims recite methods of administering paclitaxel comprising administering paclitaxel over a period of "7 days or more", wherein the amount of paclitaxel is "about 1% to about 20% of the conventional dose" of paclitaxel (claim 90) or "about 1% to about 10% of the conventional dose" of paclitaxel (claim 111).

Fennelly *et al.* teach administration of paclitaxel in doses of 40, 50, 60, 80, and 100 mg/m^2 to ovarian cancer patients (Abstract). These doses anticipate the instantly claimed doses of "*about* 1 % to *about* 20% of the conventional dose of paclitaxel" (claim 90) and "*about* 1 % to *about* 10% of the conventional dose of paclitaxel" (claim 111). Paclitaxel was administered via a 1-hour infusion thus anticipating the instantly claimed "systemically" and "intravenously" as recited in claims 95, 97, 114, and 116 (*id.*). A "one-hour infusion" also meets the limitation "continuously" as recited in claims 106 and 125. The infusions were administered "weekly" for an average of 10 weeks thus meeting the limitations of claims 91-92, 107-108, 112, and 126-127 (*id.*).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 99, 101, 118, and 120 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fennelly *et al.* as applied to claims 90-95, 97-98, 100, 103, 105-108, 110-114, 116-117, 119, 122, 124-127, and 129 above, and further in view of WO 98/14174 (Published April 9, 1998) (Reference 46 on IDS filed 9/4/2007).

Instant claims 99, 101, 118, and 120 recite administration of paclitaxel in a slow release delivery vehicle and/or a colloidal dispersion system comprising nanocapsules.

Fennely *et al.* teach as discussed *supra*. The reference does not teach the administration of paclitaxel in a colloidal dispersion system comprising nanocapsules or a slow release delivery vehicle.

However, WO '174 teaches compositions and methods for the *in vivo* delivery of substantially insoluble pharmacologically active agents (such as paclitaxel) in which the active agent is delivered in the form of suspended particles coated with a protein (Abstract). The particulate system of the invention can be converted into a redispersible dry powder comprising **nanoparticles** of water-insoluble drug coated with a protein, and free protein to which molecules of the active agent are bound (*id.*). Invention colloidal systems may be prepared without the use of conventional surfactants and in a preferred embodiment, the invention methods is used to prepare extremely small particles which can be sterile-filtered (page 1, lines 13-18). The nanoparticles of the invention provide a pre-programmed duration of action, ranging from days to weeks to months from a single injection, thus meeting the limitation "slow release delivery vehicles" as recited in claims 99 and 118 (page 2, lines 14-16).

Thus, it would have been *prima facie* obvious to one ordinary skill in the art to administer paclitaxel in nanoparticles in order to provide a pre-programmed duration of action and to decrease toxicity associated with conventional paclitaxel administration methods.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Scope and contents of prior art

The prior art teaches methods of administering paclitaxel comprising administering paclitaxel in doses of 40, 50, 60, 80, and 100 mg/m^2 via a 1-hour infusion weekly for 10 weeks. The prior art also motivates and suggests administering paclitaxel in nanoparticles in order to provide a pre-programmed duration of action and to decrease toxicity associated with conventional paclitaxel administration methods.

Differences between prior art and claims

The prior art does not explicitly teach administering paclitaxel in nanoparticles or in a slow release delivery vehicle using the administration regimen instantly claimed.

Level of ordinary skill in the art

The level of ordinary skill in the art is high, generally that of a Ph.D. or M.D. with at least several years of experience in drug delivery methods.

Objective evidence and motivation

There is no evidence of record that one skilled in the art would not have found the instantly claimed delivery vehicles *prima facie* obvious. Slow release delivery vehicles and colloidal dispersion systems such as nanoparticles are routinely used to deliver pharmacologically active agents. Accordingly, use of these vehicles to deliver paclitaxel would have been obvious to the skilled artisan. At the time of the invention, there was a recognized need in the art – that being an administration regimen for paclitaxel that would be clinically effective and at the same time non-toxic. One skilled in the art is faced with a finite number of predictable solutions for delivering paclitaxel to human patients. For example, one could modify the administration schedule (*i.e.*, longer or shorter duration between infusions), dose (*i.e.*, higher or lower doses), and/or length of infusion (*i.e.*, longer or shorter infusion duration). Further, delivery vehicles for administration of pharmacologically active agents are limited in number (*e.g.*, aqueous solutions, emulsions, liposomes, tablets, etc.). Given the finite number of predictable solutions for delivering active agents, one skilled in the art could have pursued the known options within his or her technical grasp with a reasonable expectation of success. In other words, one skilled in the art could readily formulate paclitaxel in a slow release delivery vehicle or in nanoparticles and administered these formulations to patients with a reasonable expectation that the formulations would have been clinically effective.

Claims 99-104 and 118-123 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fennelly *et al.* as applied to claims 90-95, 97-98, 100, 103, 105-108, 110-114, 116-117, 119, 122, 124-127, and 129 above, and further in view of U.S. Patent No. 6,211,171 (Issued Apr. 3, 2001; Filed May 19, 1998) (newly cited).

Instant claims 99-104 and 118-123 recite administration of paclitaxel in a slow release delivery vehicle, a colloidal dispersion system, in a polymer of stabilized crystals and in colloidal dispersion systems comprising nanocapsules, microspheres, liposomes, or oil-in-water emulsions.

Fennely *et al.* teach as discussed *supra*. The reference does not teach the administration of paclitaxel in a slow release delivery vehicle, in a polymer of stabilized crystals or in colloidal dispersion systems comprising nanocapsules or microspheres

However, U.S. '171 teaches methods for the *in vivo* delivery of antidepressants (Abstract). At column 11, lines 1-17, compositions formulated for local injections are taught which generally comprise a physiologically compatible saline solution and may optionally be encapsulated in a slow release delivery vehicle suitable for local injection, such as a colloidal dispersion system or in polymer stabilized crystals. Colloidal dispersion systems include nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. The preferred colloidal system of this invention is a liposome or microsphere. Liposomes are artificial membrane vesicles which are useful as slow release delivery vehicles when injected or implanted, or when contained within a topical preparation.

Thus, it would have been *prima facie* obvious to one ordinary skill in the art to formulate paclitaxel in a composition suitable for local injection, such as those compositions taught in U.S. '171.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Scope and contents of prior art

The prior art teaches methods of administering paclitaxel comprising administering paclitaxel in doses of 40, 50, 60, 80, and 100 mg/m^2 via a 1-hour infusion weekly for 10 weeks. The prior art also teaches compositions suitable for local injection of active agents comprising a physiologically compatible saline solution and may optionally be encapsulated in a slow release delivery vehicle suitable for local injection, such as a colloidal dispersion system or in polymer stabilized crystals.

Differences between prior art and claims

The prior art does not explicitly teach administering paclitaxel in a colloidal dispersion system or in polymer-stabilized crystals using the administration regimen instantly claimed.

Level of ordinary skill in the art

The level of ordinary skill in the art is high, generally that of a Ph.D. or M.D. with at least several years of experience in drug delivery methods.

Objective evidence and motivation

There is no evidence of record that one skilled in the art would not have found the instantly claimed delivery vehicles *prima facie* obvious. Compositions formulated for local injections, which generally comprise a physiologically compatible saline solution and may optionally be encapsulated in a slow release delivery vehicle suitable for local injection, such as a colloidal dispersion system or in polymer stabilized crystals were known in the art. Such colloidal dispersion systems include nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes as instantly claimed. Accordingly, use of these vehicles to deliver paclitaxel would have been obvious to the skilled artisan. At the time of the invention, there was a recognized need in the art – that being an administration regimen for paclitaxel that would be clinically effective and at the same time non-toxic. One skilled in the art is faced with a finite number of predictable solutions for delivering paclitaxel to human patients. For example, one could modify the administration schedule (*i.e.*, longer or shorter duration between infusions), dose (*i.e.*, higher or lower doses), and/or length of infusion (*i.e.*, longer or shorter infusion duration). Further, delivery vehicles for administration of pharmacologically active agents are limited in number (*e.g.*, aqueous solutions, emulsions, liposomes, tablets, etc.). Given the finite number of predictable solutions for delivering active agents, one skilled in the art could have pursued the known options within his or her technical

grasp with a reasonable expectation of success. In other words, one skilled in the art could readily formulate paclitaxel in a slow release delivery vehicle suitable for local injection, such as a colloidal dispersion system or in polymer stabilized crystals, and administered these formulations to patients with a reasonable expectation that the formulations would have been clinically effective.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

U.S. Non-Provisional Application No. 11/644,850

Claims 90-98, 105-117, and 124-129 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 11/644,850. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed methods of the 11/644/850 patent fully

encompass the instantly claimed subject matter and are generic to the claimed methods of administration.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

November 6, 2007

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER